AMENDMENTS TO THE CLAIMS:

This listing of claims will replace prior versions and listings of claims in the application:

Listing of claims:

Claims 30-32, 36-38, 45-47, 51-53, 56, 66, 92-97 and 100-103 have been amended as follows and claims 114 to 119 are new: Underlines indicate insertions and ~~strikeouts~~ indicate deletions.

1-29. (Cancelled)

30. (Currently amended) A soluble ~~fragment~~ polypeptide of a subtilisin-kexin isoenzyme named SKI-1 which has the amino acid sequence defined by amino acids 187 to 996 of ~~any one of~~ SEQ ID NO~~s: 2, 4 and~~ 6, ~~or an amino acid sequence from another mammalian species corresponding to the sequence of said amino acids 187 to 996 , which is enzymatically active~~.

31. (Currently amended) A polypeptide ~~fragment~~ of a subtilisin-kexin isoenzyme named SKI-1, which has the amino acid sequence defined by amino acids 17 to 137 of ~~any one of~~ SEQ ID NO~~s: 2, 4 and~~ 6, ~~or an amino acid sequence from another mammalian species corresponding to the sequence of said amino acids 17 to 137or a part thereof,~~ which is capable of binding with amino acids 17 to 1052 of SKI-1.

32. (Currently amended) The polypeptide ~~fragment~~ of claim 31, wherein said ~~part~~ polypeptide has a molecular weight of about 14 kDa when resolved by SDS-PAGE on a 8% gel and forms a ~~tight~~ complex with the soluble fragment of SKI-1.

33. (cancelled)

34. (cancelled)

35. (cancelled)

36. (Currently amended) An isolated nucleic acid encoding a polypeptide ~~fragment~~ as defined in claim 30.

37. (Currently amended) An isolated nucleic acid encoding a polypeptide ~~fragment~~ as defined in claim 31.

38. (Currently amended) An isolated nucleic acid encoding a polypeptide ~~fragment~~ as defined in claim 32.

39. (cancelled).

40. (Previously presented) A recombinant vector comprising the nucleic acid defined in claim 36.

41. (Previously presented) The recombinant vector of claim 40, which is an expression vector.

42. (Previously presented) The recombinant vector of claim 41, which comprises a promoter expressible in a target cell wherein expression of said nucleic acid is desirable.

43. (Previously presented) The recombinant vector of claim 42, which comprises an inducible promoter.

44. (Previously presented) A recombinant host cell comprising the recombinant vector defined in claim 40.

45. (Currently amended) A method of producing a fragment of SKI-1 enzyme, which comprises the steps of:

culturing a recombinant host cell expressing a nucleic acid as defined in claim 36 in ~~a cell growth and~~an expression-supportive culture medium; and recovering said fragment of SKI-1 in the culture medium.

46. (Currently amended) A method for cleaving a substrate for SKI-1 enzyme, which comprises the step of:

a) contacting said substrate ~~with a SKI-1 enzyme which has~~ 1) a ~~SKI-1~~ soluble fragment of a subtilisin-kexin isoenzyme ~~named SKI-1~~ which has the amino acid sequence defined by amino acids 187-996 of ~~any one of~~ SEQ ID NO~~s: 2, 4 and~~ 6, ~~or 2) an amino acid sequence from another mammalian species corresponding to the sequence of said amino acids 187 to 996~~; 3~~2~~) a catalytic part of 1) ~~or 2)~~ or 3~~4~~) a complex as defined in claim 32, for a time sufficient and in conditions adequate for such cleavage to occur,

with the proviso that said substrate is not a sterol-regulatory element-binding protein (SREBP) and is not SKI-1.

47. (Currently amended) A method for producing a protein or a peptide from a precursor which is an enzymatic substrate for SKI-1 enzyme, which comprises the steps of:

a) contacting said proteic precursor with ~~a SKI-1 enzyme which has~~ 1) a ~~SKI-1~~ soluble fragment of a subtilisin-kexin isoenzyme ~~named SKI-1~~ which has the amino acid sequence defined by amino acids 187-996 of ~~any one of~~ SEQ ID NO~~s: 2, 4 and~~ 6, ~~or 2) an amino acid sequence from another mammalian species corresponding to the sequence of said amino acids 187 to 996 which is enzymatically active~~; or 3~~2~~) a catalytic part of 1) ~~or 2)~~; or 4~~3~~) a complex as defined in claim 32, for a time sufficient and in conditions adequate for such cleavage to occur; and

b) recovering said protein or peptide;

with the proviso that said substrate is not a sterol-regulatory element-binding protein (SREBP) and is not SKI-1.

48. (Previously presented) The method of claim 47, which takes place in a cell or in the presence of a cellular population and wherein step a) comprises the step of transfecting a cell with a nucleic acid expressing said SKI-1 enzyme.

49. (Previously presented) The method of claim 48, wherein said cell expresses said precursor or is transfected with a nucleic acid expressing said precursor.

50. (withdrawn) A method of inhibiting the activity of a subtilisin-kexin isoenzyme named SKI-1, which comprises the step of contacting SKI-1 with the inhibitor of claim 33 or isolated nucleic acid encoding the inhibitor.

51. (Currently amended) A peptide of at least 7 amino acids capable of binding to and of being cleaved by SKI-1 catalytic site, said peptide comprising a sequence as set forth in SEQ ID NO: 7 ~~comprising the following general formula: Arg Xaa_1-J Xaa_2-↓-Xaa_3-$(Z)_n$-O~~

~~wherein $Xaa_{1, 2, 3}$ and Z are any amino acid~~
~~J is an alkyl or aromatic hydrophobic amino acid~~
~~n is 1, 2 or 3~~
~~O is an acidic amino acid~~,

with the proviso that said peptide does not comprise the sequence ~~Lys-Arg-Phe-Val-Phe-Asn-Lys-Ile-Glu-~~as set forth in SEQ ID NO: 78 and with the proviso that said substrate is not a sterol-regulatory element-binding protein (SREBP) or a part thereof or SKI-1 or a part thereof.

52. (Currently amended) A peptide as defined in claim 51, wherein ~~Xaa_2 is Lys, Leu, Phe or Thr.~~said peptide comprises the sequence as set forth in SEQ ID NO: 8.

53. (Currently amended) A peptide as defined in claim 52 which has the sequence: as set forth in SEQ ID NO: 77~~H_2N-Val-Phe-Arg-Ser-Leu-Lys-Tyr-Ala-Glu-Ser-Asp-COOH~~.

54. (Previously presented) A peptide as defined in claim 51 which is labelled.

55. (Previously presented) A peptide as defined in claim 54 which is fluorogenic.

56. (Currently amended) A peptide as defined in claim 55 which is Abz-~~Val-Phe-Arg-Ser-Leu-Lys-Tyr-Ala-Glu-Ser-Asp~~SEQ ID NO: 77-Tyr(NO_2),
wherein Abz is orthoaminobenzoic acid, and
Tyr(NO_2) is 3-nitrotyrosine.

57-58. (Cancelled)

59. (Previously presented) A method for screening for a polypeptide that has the activity of a subtilisin-kexin isoenzyme named SKI-1, the method comprising the steps of:

contacting the peptide of claim 51 to a test polypeptide under conditions that allow cleavage of the peptide by a SKI-1; and

detecting the cleavage of the peptide wherein the presence of the cleavage indicates that the polypeptide has SKI-1 activity.

60. (Previously presented) A method for monitoring the activity of a subtilisin-kexin isoenzyme named SKI-1 comprising the steps of:

contacting a sample having or suspected of having SKI-1 activity with the peptide of claim 51; and

monitoring the cleavage of the peptide.

61. (withdrawn) A method for screening inhibitors or substrates of a subtilisin-kexin isoenzyme named SKI-1 comprising the steps of:

contacting the protein which has SKI-1 activity with the peptide of claim 51 in the presence of a test compound under conditions that allow cleavage of the peptide the protein with SKI-1 activity;

determining the cleavage of the peptide; and

comparing the cleavage of the peptide with that of a control group in which the protein with SKI-1 activity is contacted with the peptide of claim 51 in the absence of the test compound under the same conditions wherein a lower than control cleavage rate indicates that the test compound is an inhibitor or substrate of SKI-1.

62. (withdrawn) A method for treating a disease related to an overexpression of a SKI-1 or a SKI-1 substrate in a human or non-human animal, the method comprising the step of:

administering to the human or non human animal an inhibitor of the activity of SKI-1 in an amount sufficient to inhibit the activity.

63. (withdrawn) The method of claim 62, wherein said disease is associated with any one of hypercholesterolemia, high levels of fatty acids, lipids or farnesyl pyrophosphate, liver steatosis, Ras-dependent cancer, restenosis and amyloid protein formation.

64. (withdrawn) The method of claim 62, wherein said inhibitor is defined in claim 31.

65. (Previously presented) A composition comprising a SKI-1 fragment as defined in claim 30.

66. (Currently amended) A method for cleaving a precursor which is SKI-1 substrate, the method comprising the steps of:

providing a SKI-1 enzyme as encoded by a nucleic acid having a nucleotide sequence of ~~nucleotides 469 to 3573 of SEQ ID NO: 1, nucleotides 59 to 3163 of SEQ ID NO: 3 or~~ nucleotides 548 to 3652 of SEQ ID NO: 5,

a catalytic part of SKI-1 enzyme that is unique to SKI-1 enzyme and encoded by the corresponding sequence of SEQ ID NOs: ~~1, 3 or~~ 5,

~~or an active variant of the SKI-1 enzyme or the catalytic part, wherein the nucleotide sequence that encodes the variant shares at least 70% homology with a~~

~~nucleotide sequence on SEQ ID NOs: 1, 3 or 5 and hybridizes to SEQ ID NOs: 1, 3 or 5 under stringent hybridization conditions,~~

and contacting the precursor with the SKI-1 enzyme, the catalytic part of SKI-1, or the active variant of the SKI-1 enzyme of the catalytic part under conditions that allow the cleavage of the precursor, with the proviso that said substrate is not a sterol-regulatory element-binding protein (SREBP) and is not SKI-1.

67. (Previously presented) A composition comprising a SKI-1 fragment as defined in claim 31.

68. (Previously presented) A composition comprising a SKI-1 fragment as defined in claim 32.

69. (cancelled).

70. (cancelled).

71. (cancelled).

72. (Previously presented) A composition comprising a nucleic acid as defined in claim 36.

73. (Previously presented) A composition comprising a nucleic acid as defined in claim 37.

74. (Previously presented) A composition comprising a nucleic acid as defined in claim 38.

75-79. (Cancelled)

80. (Previously presented) A composition comprising a recombinant vector as defined in claim 40.

81. (Previously presented) A composition comprising a recombinant vector as defined in claim 41.

82. (Previously presented) A composition comprising a recombinant vector as defined in claim 42.

83. (Previously presented) A composition comprising a recombinant vector as defined in claim 43.

84. (withdrawn) A method of inhibiting SKI-1 activity comprising contacting a prosegment of about 24kDa of a subtilisin-kexin isoenzyme named SKI-1, with SKI-1.

85. (withdrawn) A method as recited in claim 84, wherein the prosegment is a native prosegment and has the amino acid sequence defined by amino acids 17 to 186

of SEQ ID NO: 6 or an amino acid sequence from another mammalian species corresponding to the sequence of said amino acids 17 to 186.

86. (withdrawn) The method of claim 84, wherein the prosegment amino acid sequence is modified to prevent further enzymatic processing in a cell expressing said prosegment.

87. (withdrawn)The method as recited in claim 86, wherein said amino acid sequence is modified at the internal primary cleavage site to prevent the creation of a 14kDa N-terminal fragment.

88. (withdrawn) The method of claim 86, wherein the amino acid sequence is modified by amino acid substitution, deletion, rearrangement or addition.

89. (withdrawn) The method of claim 88, wherein the amino acid is defined by amino acids 17 to 188 of SEQ ID NO: 6 or an amino acid sequence from another mammalian species corresponding to the sequence of said amino acids 17 to 188.

90. (withdrawn) The method of claim 88, wherein the amino acid is defined by amino acids 1 to 197 of SEQ ID NO: 6 or an amino acid sequence from another mammalian species corresponding to the sequence of said amino acids 17 to 197.

91. (withdrawn) The method of claim 88, wherein the amino acid is defined by amino acids 1 to 169 of SEQ ID NO: 6 or an amino acid sequence from another mammalian species corresponding to the sequence of said amino acids 17 to 169.

92. (Currently amended) A purified polypeptide defined by amino acids 1 to 188 of SEQ ID NO: 6 ~~or by an amino acid sequence from another mammalian species corresponding to the sequence of said amino acids 1 to 188~~.

93. (Currently amended) A purified polypeptide defined by amino acids 1 to 197 of SEQ ID NO: 6 ~~or by an amino acid sequence from another mammalian species corresponding to the sequence of said amino acids 1 to 197~~.

94. (Currently amended) A purified polypeptide defined by amino acids 1 to 169 of SEQ ID NO: 6 ~~or by an amino acid sequence from another mammalian species corresponding to the sequence of said amino acids 1 to 169~~.

95. (Currently amended) A purified polypeptide defined by amino acids 17 to 188 of SEQ ID NO: 6 ~~or by an amino acid sequence from another mammalian species corresponding to the sequence of said amino acids 17 to 188~~.

96. (Currently amended) A purified polypeptide defined by amino acids 17 to 197 of SEQ ID NO: 6 ~~or by an amino acid sequence from another mammalian species corresponding to the sequence of said amino acids 17 to 197~~.

97. (Currently amended) A purified polypeptide defined by amino acids 17 to 169 of SEQ ID NO: 6 ~~or by an amino acid sequence from another mammalian species corresponding to the sequence of said amino acids 17 to 169~~.

98. (Previously presented) An isolated nucleic acid encoding a polypeptide as defined in claim 92.

99. (Previously presented) An isolated nucleic acid encoding a polypeptide as defined in claim 93.

100. (Currently amended) An isolated nucleic acid encoding a polypeptide ~~fragment~~ as defined in claim 94.

101. (Currently amended) An isolated nucleic acid encoding a polypeptide ~~fragment~~ as defined in claim 95.

102. (Currently amended) An isolated nucleic acid comprising a sequence that encodes a polypeptide ~~fragment~~ as defined in claim 96.

103. (Currently amended) An isolated nucleic acid encoding a polypeptide ~~fragment~~ as defined in claim 97.

104. (Previously presented) A composition comprising a polypeptide as defined in claim 92.

105. (Previously presented) A composition comprising a polypeptide as defined in claim 93.

106. (Previously presented) A composition comprising a polypeptide as defined in claim 94.

107. (Previously presented) A composition comprising a polypeptide as defined in claim 95.

108. (Previously presented) A composition comprising a polypeptide as defined in claim 96.

109. (Previously presented) A composition comprising a polypeptide as defined in claim 97.

110. (withdrawn) A method of inhibiting SKI-1 activity comprising contacting a cell with a prosegment having the amino acid sequence defined by amino acids 1 to 186 of SEQ ID NO: 6 or an amino acid sequence from another mammalian

species corresponding to the sequence of said amino acids 1 to 186 of a subtilisin-kexin isoenzyme named SKI-1, with SKI-1.

111. (withdrawn) A method of inhibiting SKI-1 activity comprising contacting a cell with a prosegment having the amino acid sequence defined by amino acids 1 to 188 of SEQ ID NO: 6 or an amino acid sequence from another mammalian species corresponding to the sequence of said amino acids 1 to 188 of a subtilisin-kexin isoenzyme named SKI-1, with SKI-1.

112. (withdrawn) A method of inhibiting SKI-1 activity comprising contacting a cell with a prosegment having the amino acid sequence defined by amino acids 1 to 197 of SEQ ID NO: 6 or an amino acid sequence from another mammalian species corresponding to the sequence of said amino acids 1 to 197 of a subtilisin-kexin isoenzyme named SKI-1, with SKI-1.

113. (withdrawn) A method of inhibiting SKI-1 activity comprising contacting a cell with a prosegment having the amino acid sequence defined by amino acids 1 to 169 of SEQ ID NO: 6 or an amino acid sequence from another mammalian species corresponding to the sequence of said amino acids 1 to 169 of a subtilisin-kexin isoenzyme named SKI-1, with SKI-1.

114. (New) A recombinant vector comprising the isolated nucleic acid defined in claim 98.

115. (New) A recombinant vector comprising the isolated nucleic acid defined in claim 99.

116. (New) A recombinant vector comprising the isolated nucleic acid defined in claim 100.

117. (New) A recombinant vector comprising the isolated nucleic acid defined in claim 101.

118. (New) A recombinant vector comprising the isolated nucleic acid defined in claim 102.

119. (New) A recombinant vector comprising the isolated nucleic acid defined in claim 103.